(B) a second chimeric polypeptide comprising a second fragment of an enzyme or a modulating substance capable of activating the enzyme;

wherein the first fragment is fused to a molecule of interest and the second fragment or modulating substance is fused to a target ligand;

(2) contacting the molecule of interest and the target ligand;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1); and,

(4) triggering transcriptional activation;

wherein activity of the enzyme is restored by *in vivo* interaction between the molecule of interest and the target ligand, which generates the amplified signal in (3).

11. (AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification comprises the production of a signaling molecule.

12. (AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the transcriptional activation results in expression of a reporter gene.

14. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance.

15. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the target ligand is selected from the group consisting of protein, peptide, polypeptide, receptor, antigen, antibody, DNA binding protein, glycoprotein, lipoprotein, and recombinant protein.

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17. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the interaction between the molecule of interest and the target ligand is detected by signal amplification that triggers transcriptional activation, and is quantified by measuring the synthesis of a signaling molecule or expression of a reporter gene.

18. (AMENDED) The method of selecting a molecule of interest as claimed in claim 11, wherein the signaling molecule is a component of a cAMP signaling cascade reaction.

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19. (AMENDED) The method of selecting a molecule of interest as claimed in claim 11, wherein the signaling molecule is a component of a cGMP signaling cascade reaction.

20. (AMENDED) The method of selecting a molecule of interest as claimed in claim 12, wherein the reporter gene is a gene with a selectable phenotype.

21. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein an amino acid sequence of the molecule of interest is mutated compared to an amino acid sequence of the wild type molecule and said molecule of interest is tested for its ability to interact with the target ligand.

22. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the selection is performed in a bacterial strain.

25. (TWICE AMENDED) A method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest wherein the method comprises:

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(1) providing a signal amplification system that comprises a bacterial multi-hybrid system of at least two chimeric polypeptides containing:

(A) a first chimeric polypeptide comprising a first fragment of an enzyme;

(B) a second chimeric polypeptide comprising a second fragment of the enzyme or a modulating substance capable of activating said enzyme;

wherein the first fragment is fused to a molecule of interest and the second fragment or the modulating substance is fused to a target ligand;

(2) contacting the molecule of interest and the target ligand in the presence of the substance;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1);

(4) triggering or abolishing transcriptional activation,

wherein the activity of the enzyme is restored by *in vivo* interaction between the molecule of interest and the target ligand, which generates the amplified signal in (3); and

(5) comparing said signal amplification with the one obtained from an identical signal amplification system in the absence of the substance, wherein a difference in the signal amplification in the presence and absence of the substance indicates that the substance stimulates or inhibits the interaction between the target ligand and the molecule of interest.

26. (AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid

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system of at least two distinct fragments of an enzyme, wherein the enzymatic activity is restored by the interaction between the molecule of interest and the target ligand.

27. (AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance.

28. (TWICE AMENDED) The method of screening for a substance that stimulates the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification comprises the production of a signaling molecule.

29. (TWICE AMENDED) The method of screening for a substance that inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification is blocked or partially abolished.

30. (TWICE AMENDED) The method of screening for a substance that stimulates the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the transcriptional activation results in reporter gene expression.

31. (TWICE AMENDED) The method of screening for a substance that inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the transcriptional activation results in a reporter gene expression which is blocked or partially abolished.

32. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest

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as claimed in claim 25, wherein the target ligand is selected from the group consisting of receptor, antigen, antibody, DNA binding protein, glycoprotein and lipoprotein.

34. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule is a component of a cAMP signaling cascade reaction.

35. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule is a component of a cGMP signaling cascade reaction.

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36. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 30, wherein the reporter gene is a gene with a selectable phenotype.

37. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the amino acid sequence of the molecule of interest is mutated compared to the amino acid sequence of the wild type molecule and said molecule of interest is tested for its ability to interact with the target ligand.

38. (TWICE AMENDED) The method of screening for a substance that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the screening is performed in a bacterial strain.

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Please add the following new claims:

--46. (NEW) The method as claimed in claim 20, wherein the reporter gene is selected from a gene for synthesis of a nutritional marker, a gene conferring resistance to an antibiotic, a gene encoding a toxin, a gene encoding a color marker, a gene encoding a phage receptor protein, and a gene encoding a fragment of a receptor of a phage receptor protein.

47. (NEW) The method as claimed in claim 46 wherein the nutritional marker is lactose or maltose.

48. (NEW) The method as claimed in claim 46 wherein the antibiotic is ampicillin, kanamycin, or tetracyclin.

49. (NEW) The method as claimed in claim 46, wherein color marker is a fluorescent marker.

50. (NEW) The method as claimed in claim 49, wherein the fluorescent marker is Green Fluorescent Protein.

51. (NEW) The method as claimed in claim 46, wherein the phage is phage λ or *lamB*.

52. (NEW) The method as claimed in claim 36, wherein the reporter gene is selected from a gene for synthesis of a nutritional marker, a gene conferring resistance to an antibiotic, a gene encoding a toxin, a gene encoding a color marker, a gene encoding a phage receptor protein, and a gene encoding a fragment of a receptor of a phage receptor protein.

53. (NEW) The method as claimed in claim 52 wherein the nutritional marker is lactose or maltose.

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54. (NEW) The method as claimed in claim 52 wherein the antibiotic is ampicillin, kanamycin, or tetracyclin.

55. (NEW) The method as claimed in claim 52, wherein color marker is a fluorescent marker.

56. (NEW) The method as claimed in claim 55, wherein the fluorescent marker is Green Fluorescent Protein.

57. (NEW) The method as claimed in claim 52, wherein the phage is phage λ or *lamB*.

58. (NEW) The method as claimed in claim 22, wherein the bacterial strain is an *E. coli* strain or a bacterial cell deficient in endogenous adenylate cyclase.

59. (NEW) The method as claimed in claim 38, wherein the bacterial strain is an *E. coli* strain or a bacterial cell deficient in endogenous adenylate cyclase.

60. (NEW) The method as claimed in claim 33, wherein the substance that increases or decreases the affinity between the target ligand and the molecule of interest is a protein, glycoprotein, or lipoprotein.

61. (NEW) The method as claimed in claim 34, wherein the signaling molecule is cAMP.

62. (NEW) The method as claimed in claim 35, wherein the signaling molecule is cGMP.

REMARKS

Claims 1-15, 17-32, and 34-45 are pending in this application, although claims 1-9, 23-24, and 39-45 have been withdrawn. Thus, claims 10-15, 17-22, 25-32, and 34-38, as well as new claims 46-62, are presented for reconsideration.

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